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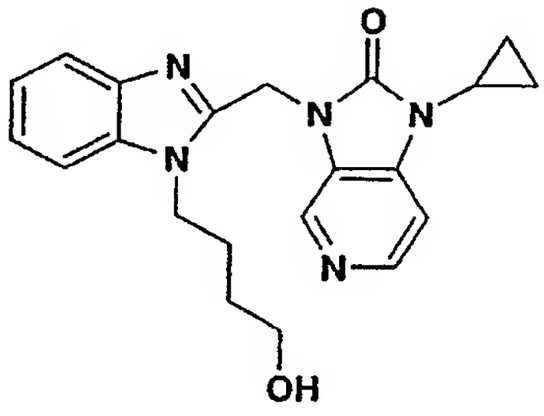
(54) Title: BIS HYDROCHLORIDE MONOHYDRATE SALT OF RSV FUSION INHIBITOR



• 2 HCl • H_2O

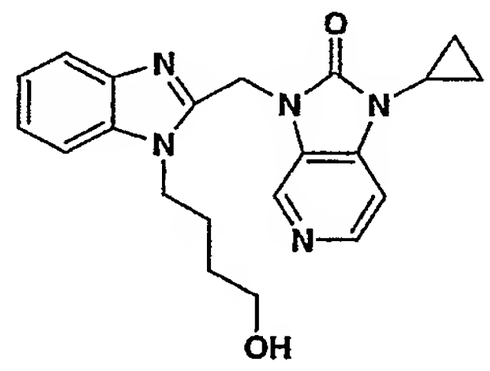
(II)

(57) Abstract: The novel crystalline bis hydrochloride monohydrate salt having the formula (II) and pharmaceutical dosage forms thereof is provided having use in the treatment of respiratory syncytial viral infection.

BIS HYDROCHLORIDE MONOHYDRATE SALT OF RSV FUSION INHIBITOR

FIELD OF THE INVENTION

The present invention provides the novel crystalline bis hydrochloride monohydrate salt of the imidazopyridine RSV (i.e., respiratory syncytial virus) Fusion Inhibitor of the formula

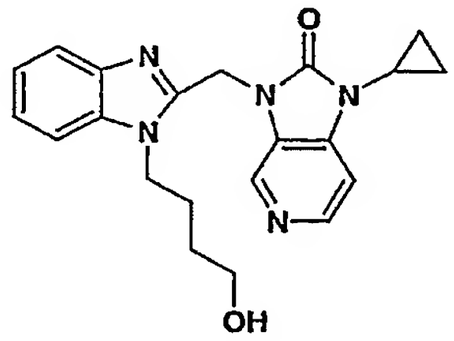


I

which exhibits superior physical stability to other salts, and significantly improved aqueous solubility/dissolution behavior and bulk characteristics compared to the free base. The bis hydrochloride monohydrate salt is thus useful for pharmaceutical dosage forms of the above indicated RSV Fusion Inhibitor, particularly for oral dosage forms.

BACKGROUND ART

Commonly-owned U.S. Patent Application No. 09/840,279 filed April 3, 2001 discloses a series of imidazopyridine and imidazopyrimidine antiviral agents reported to have a high degree of inhibitory activity against the RSV virus. One of the agents included within the scope is the compound having the structural formula

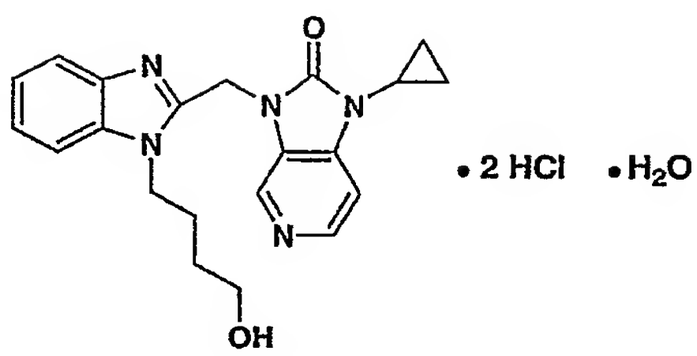


I

This application discloses the free base form of imidazopyridine derivatives such as compound **I** and also various pharmaceutically acceptable acid addition salts. While several organic and inorganic salts are mentioned as possible salt-forming agents, including hydrochloric acid, there is no mention of the particular bis hydrochloride monohydrate salt which is the subject of the present application.

SUMMARY OF THE INVENTION

The present invention provides the bis hydrochloride monohydrate salt of compound **I** above having the structural formula



II

DESCRIPTION OF THE FIGURES

FIG.1 represents differential scanning calorimetry (TA Instruments DSC 2920) showing physical stability of the bis hydrochloride monohydrate salt. The solid line represents the initial state, short dash represents 6 weeks 40°C/75% RH, long dash represents 6 weeks 50°C. After dehydration at ~100°C, melting/decomposition starts at ~180°C. No major differences can be detected between initial and stressed samples.

FIG.2 represents thermogravimetric analysis (TA Instruments TGA 2050) showing physical stability of the bis hydrochloride monohydrate salt. The solid line represents the initial state, short dash represents 6 weeks 40°C/75% RH, long dash represents 6 weeks 50°C. A weight loss of ~3.8% at ~100°C in all samples indicates the stability of the monohydrate form.

FIG.3 represent powder X-ray diffraction analysis (Rigaku Miniflex Powder X-ray Diffractometer) showing physical stability of the bis hydrochloride monohydrate salt. The patterns of initial and stressed samples are identical, indicating that no changes in the crystal structure have taken place.

FIG.4 represents thermogravimetric analysis (TA Instruments TGA 2050) showing the lack of physical stability of the mono phosphate monohydrate salt. Complete dehydration occurs at temperatures below 65°C.

FIG.5 represents differential scanning calorimetry (TA Instruments DSC 2920) showing the lack of physical stability of the mono phosphate monohydrate salt. Multiple endo- and exothermic solid phase transitions below the melting point indicate the physical instability of the salt.

DETAILED DESCRIPTION OF THE INVENTION

For the development of pharmaceutical dosage forms, the active ingredient must have acceptable bulk characteristics such as bulk density, compressibility, and flow properties. The anhydrous form P1 of the free base form of the imidazopyridine **I** displayed undesired bulk characteristics such as a very low bulk density. The bulk material was light, fluffy and difficult to handle. In addition to the anhydrous form P1 two hydrated forms P2 and P3 could be generated in a non-reproducible way. The bulk properties of P2 and P3 were not much improved compared to P1. Therefore, acid addition salts were explored by the present inventors. Based on the pKa values of the two basic functional groups of the imidazopyridine **I** (5.7 and 3.4) a number of mono and bis protonated addition salts of commonly used acids such as mono and bis methane sulfonate, mono maleate, and mono phosphate were evaluated, in addition to the mono and bis hydrochloride salts.

Crystallinity and satisfactory physical stability of the crystalline form in the solid state is a desirable property of pharmaceutical salt forms. The term physical stability indicates the ability of the salt form to retain its crystal structure including solvents of crystallization, if any, under storage/stress conditions.

Significant changes in the physical nature of the salt form as indicated by X-ray analysis or thermal methods such as differential scanning calorimetry are undesirable.

The crystalline bis hydrochloride monohydrate salt of the present invention surprisingly exhibited good bulk characteristics as well as excellent solid state physical stability when stored at 50°C or 40°C/75% relative humidity (RH) for as long as 6 weeks as shown in FIG. **1**, **2** and **3**. Differential scanning calorimetry revealed no significant changes in the thermal behavior of the stressed samples of the bis hydrochloride monohydrate salt compared to that of the unstressed sample (stored at 2-8°C in closed container). Thermogravimetric analysis as well as Karl Fischer analysis indicated that the crystal structure of the bis hydrochloride monohydrate salt retained its crystal water under above mentioned storage/stress conditions and elemental analysis of the stressed samples revealed that the salt stoichiometry of the bis hydrochloride monohydrate salt remained unchanged. No solid state transformations were observed when the bis hydrochloride monohydrate salt was suspended in water.

The mono maleate salt, and the mono phosphate monohydrate salt, on the other hand, showed significant physical instability in the solid state. The mono maleate salt, when suspended in water converted to the fumarate salt as detected by proton NMR analysis. Since fumaric acid (first pKa ~3) is a weaker acid than maleic acid (first pKa ~2) this isomerization of the acid may result in the dissociation to the free base in the solid state. The mono phosphate monohydrate salt lacked the ability to retain the crystal water under storage/stress conditions (FIG. **4**). Complete dehydration occurred at temperatures below 65°C and the obtained dehydrated form converted back to the monohydrate form when cooled back to room temperature. As an additional indication of physical instability in the solid state, the mono phosphate monohydrate salt displayed multiple solid phase transitions below its melting point, as detected by differential scanning

calorimetry and variable temperature powder X-ray analysis (FIG. 5). Methyl sulfonate salts could only be generated in the amorphous state, which is not a desirable property for pharmaceutical salt forms.

Further, an anhydrous form of the bis hydrochloride salt was shown to convert rapidly to the bis hydrochloride monohydrate salt of the present invention, when stored between 60 and 70% relative humidity at 25°C. The mono hydrochloride salt could not be generated in a reproducible way, since only mixtures of mono and bis hydrochloride salts or pure bis hydrochloride monohydrate were obtained. The propensity of a particular salt to form solvates or crystal modifications and its ability to retain the solvent of crystallization or the physical stability of crystal modifications under storage/stress conditions cannot be predicted apriori.

For the development of pharmaceutical dosage forms, particularly oral dosage forms, the active ingredient must have sufficient oral bioavailability. A comparison of the oral bioavailability of the imidazopyridine **I** in dogs revealed that compound **I** administered as the solid bis hydrochloride monohydrate salt of the present invention in capsules, had similar peak concentrations, shorter times to peak concentrations and greater exposure values than compound **I** administered as the solid free base in capsules. These pharmacokinetic data can be explained by the higher solubility/dissolution rate of the salt compared to the free base form and they support further that the bis hydrochloride monohydrate salt of the present invention has considerable advantages over the free base form of compound **I**.

The bis hydrochloride monohydrate salt may be prepared by forming a solution of the free base of compound **I** with hydrochloric acid in solvents such as acetone, isopropanol, or methanol and then isolating the so produced bis hydrochloride monohydrate salt.

Because of its bioavailability as well as good crystallinity and stability, the bis hydrochloride monohydrate salt is very useful in preparing oral dosage forms of compound **I**. An example is given below that illustrates the preparation of representative oral formulations.

BIOLOGICAL ACTIVITY

The antiviral activity of these compounds against respiratory syncytial virus was determined in HEp-2 (ATCC CCL 23) cells that were seeded in 96 well microtiter plates at $1.5x10^4$ cells/100 µL/well in DMEM (Dulbecco's Modified Eagle's Medium) supplemented with penicillin, streptomycin, glutamine, and 10% fetal bovine serum. The cells were incubated overnight at 37 °C, the culture medium was removed, and cells were infected (100 µL volume in medium containing 2% fetal bovine serum) with respiratory syncytial virus Long strain at 5000 plaque forming units/mL. The compounds, 100 µL at appropriate dilution, were added to the cells 1 hour post infection. After incubation for 4 days at 37 °C, the plates were stained with MTT solution (3-[4,5-dimethlythiazol-2-yl]-2,5-diphenyltetrazolium bromide) and incubated for 4 hours at 37 °C. The media was aspirated from the cells and 100 µL/well of acidified isopropanol (per liter: 900 mL isopropanol, 100 mL Triton X100, and 4 mL conc. HCl) was added. Plates were incubated for 15 minutes at room temperature with shaking, and an optical density (OD 540) reading at 540 nanometer (nm) was obtained. The optical density reading is proportional to the number of viable cells. The increase in the number of viable cells reflects the protective, antiviral activity of the compound. Assays comparing MTT staining in uninfected cells containing compound with uninfected cells in the absence of compound provide a measure of cellular toxicity. The control compound in this assay is Ribavirin which exhibits 100% cell protection at 2.5 µg/mL (corresponding to 10.2 µM).

The antiviral activity of compounds, designated as EC_{50}, is presented as a concentration that produces 50% cell protection in the assay. The bis-HCl mono-hydrate salt, compound **II**, disclosed in this application shows antiviral activity with EC_{50} of 0.06 μM. Ribavirin has an EC_{50} of 3 μM in this assay.

DESCRIPTION OF SPECIFIC EMBODIMENTS

Example 1

Preparation of bis hydrochloride monohydrate salt compound II from isopropanol/water/acetone

Free base compound **I** (100.0 g, 0.265 mol) was charged into a three-neck round bottom flask with mechanic stirrer and condenser. Isopropanol (400.6 ml) and water (75.0 ml) were added to give a think slurry. Concentrated HCl solution (37% aq., 47.8 ml, 2.2 eq) was added to the mixture. The mixture was heated to 60°C to form a clear solution. Then acetone (550 ml) was slowly added, while the temperature was maintained at 60°C. The mixture was stirred at 60°C for one hour before it was slowly cooled to 20-25°C. The mixture was stirred at 20-25°C for another 2 hours. The solid was filtered, washed with acetone (2x302.5 ml), and dried under vacuum overnight to give 119.3 g (96%) of the bis-HCl mono-hydrate salt compound **II**.

Anal. Calcd. $C_{21}H_{23}N_5O_2.2.0\ HCl.1.0\ H_2O$: C, 53.85; H, 5.81; N, 14.95; Cl, 15.13; H_2O, 3.8. Found: C, 53.73; H, 5.75; N, 14.96; Cl, 14.80; H_2O, 3.8 (KF).

Example 2

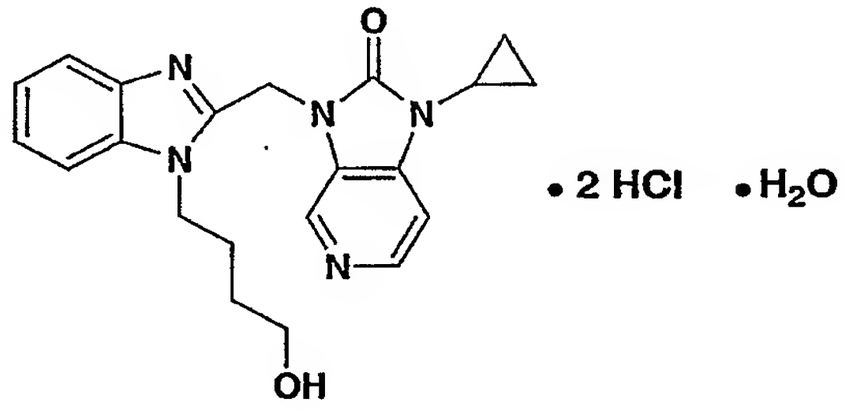
Preparation of Capsule Formulations of the bis hydrochloride monohydrate salt

Capsules (10 and 50 mg free base equivalent) are provided for oral administration in which the capsule size is #0, gray, opaque, hard gelatin capsule containing the bis hydrochloride monohydrate salt of formula **II** formulated as dry granulation with microcrystalline cellulose, pregelatinized starch, sodium starch glyconate, and magnesium stearate.

CLAIMS

We claim:

1. The bis hydrochloride monohydrate salt having the formula



II

2. A pharmaceutical dosage form comprising the bis hydrochloride monohydrate salt of claim 1 and a pharmaceutically acceptable carrier.

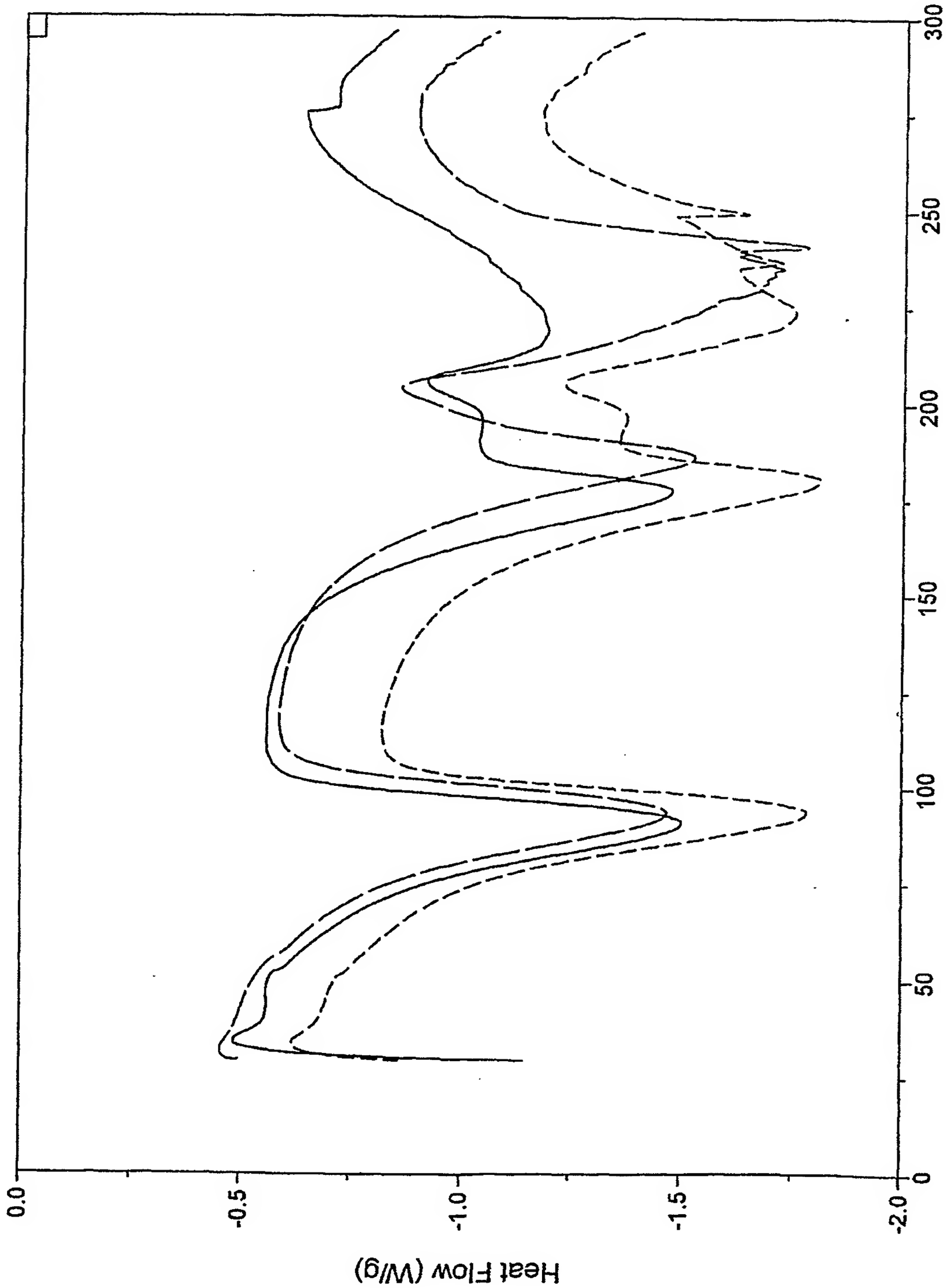

Heat Flow (W/g)
0.0
-0.5
-1.0
-1.5
-2.0
0
50
100
150
200
250
300
Temperature (°C)

FIG. 1

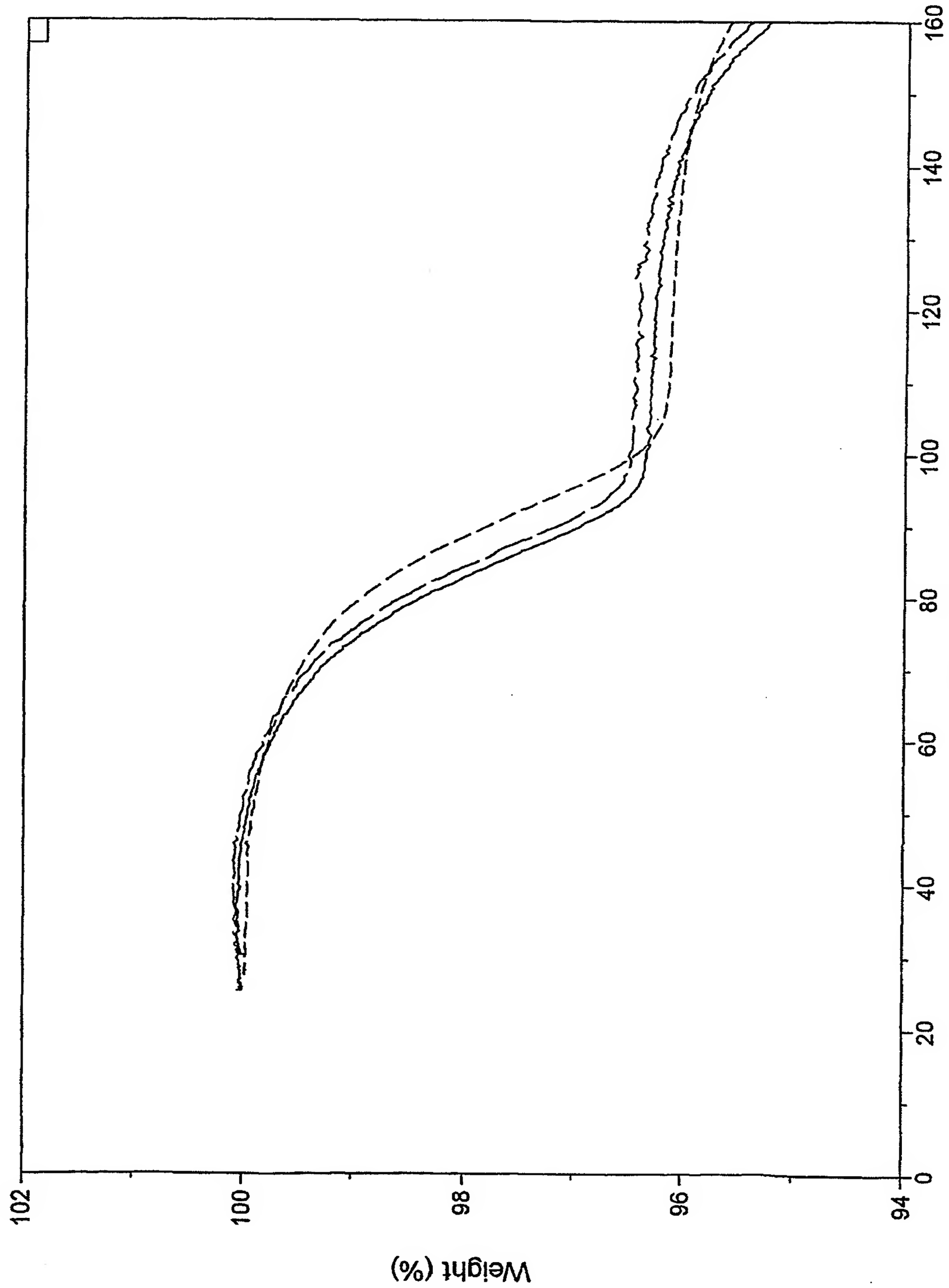

Weight (%)
102
100
98
96
94
Temperature (°C)
0
20
40
60
80
100
120
140
160

FIG. 2

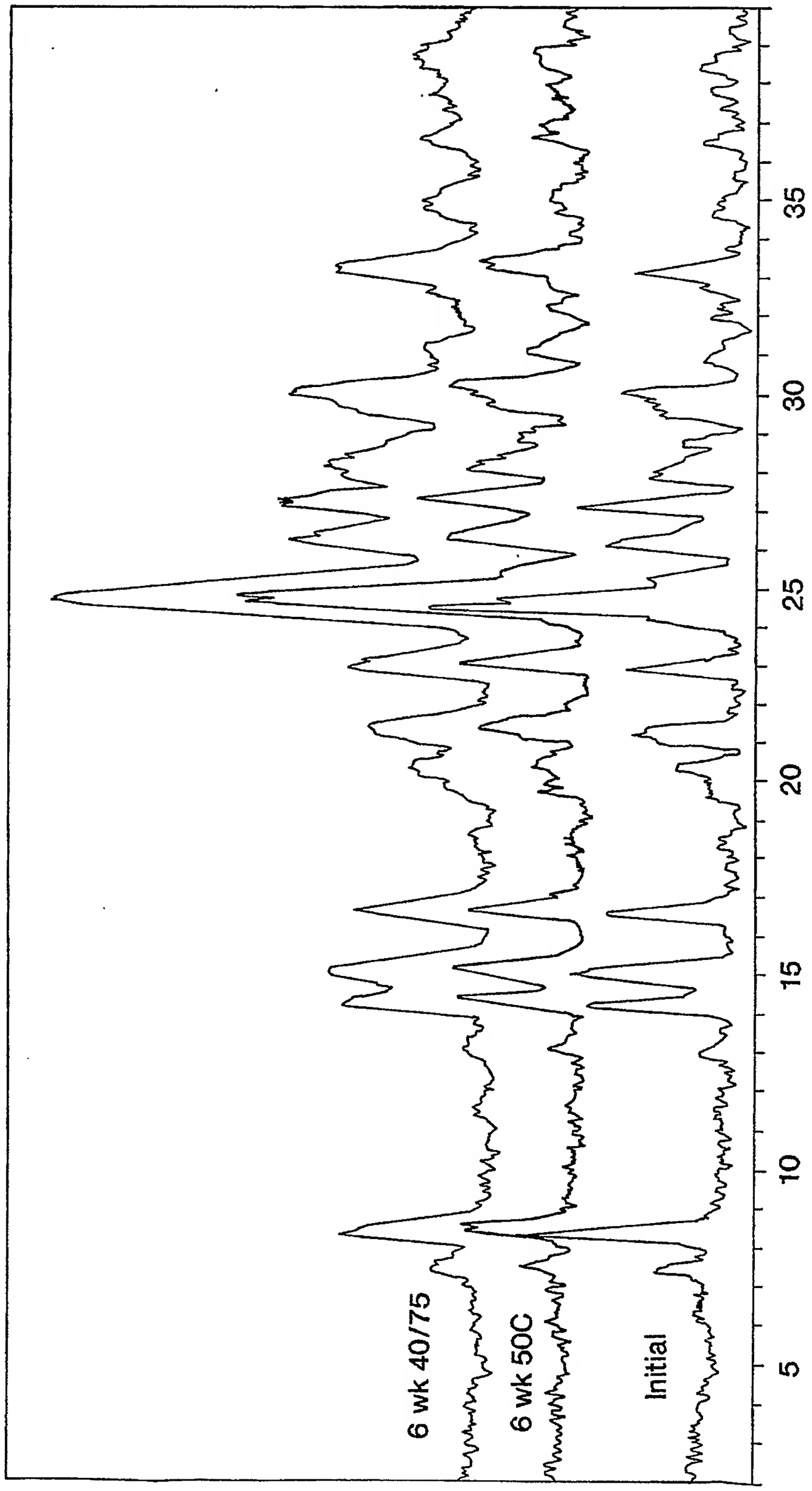


FIG. 3

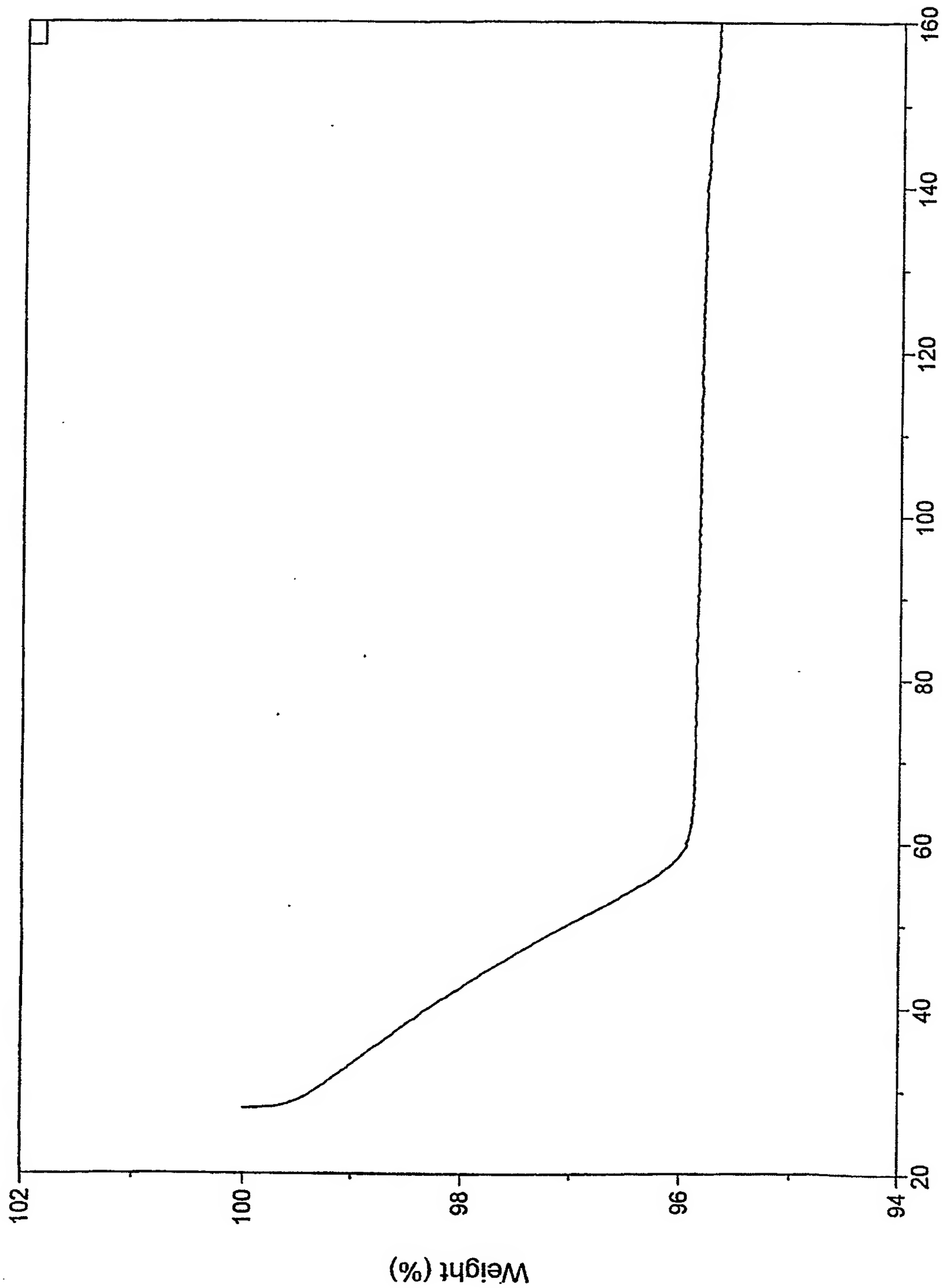

Weight (%)
102
100
98
96
94
Temperature (°C)
20
40
60
80
100
120
140
160

FIG. 4

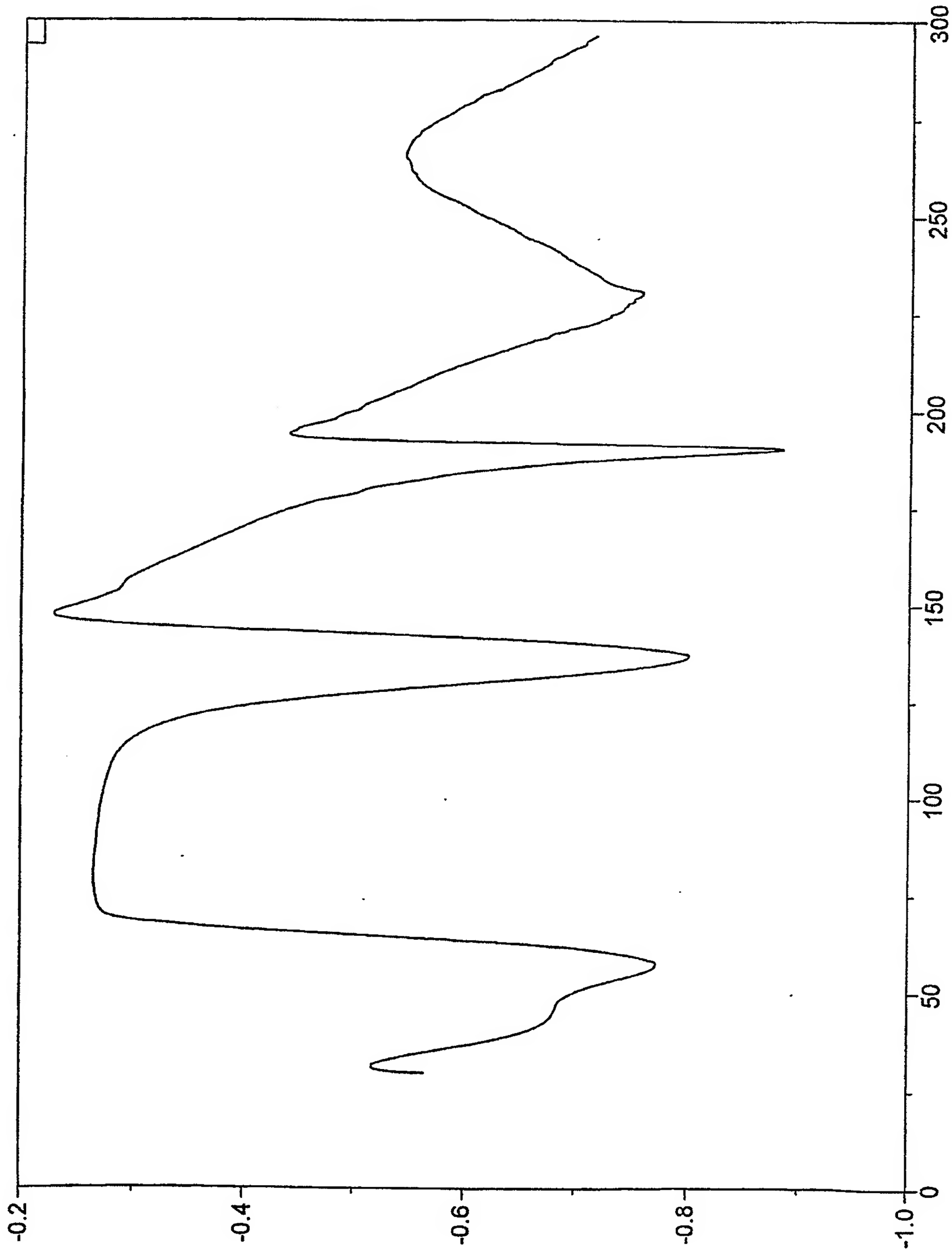

Heat Flow (W/g)
-0.2
-0.4
-0.6
-0.8
-1.0
0
50
100
150
200
250
300
Temperature (°C)

FIG. 5

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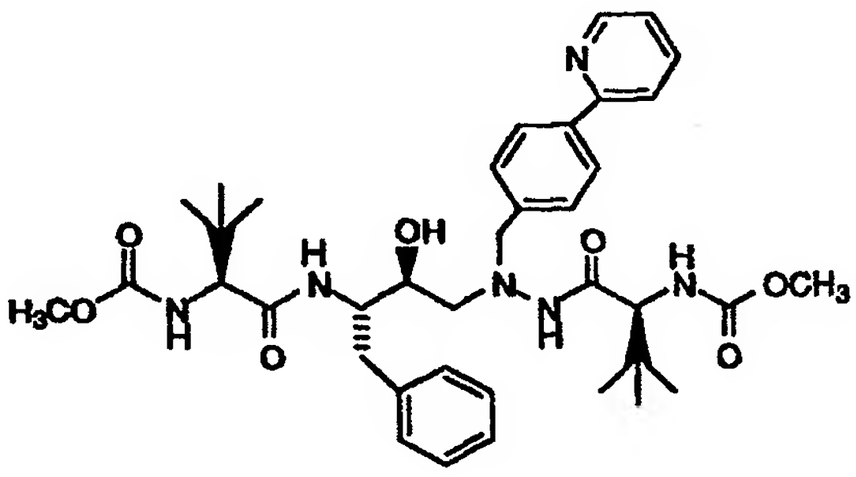
Published
With international search report.

(54) Title: BISULFATE SALT OF HIV PROTEASE INHIBITOR



(II)

(57) Abstract

The present invention provides the crystalline bisulfate salt of formula (II) which is found to have unexpectedly high solubility/dissolution rate and oral bioavailability relative to the free base form of this azapeptide HIV protease inhibitor compound.

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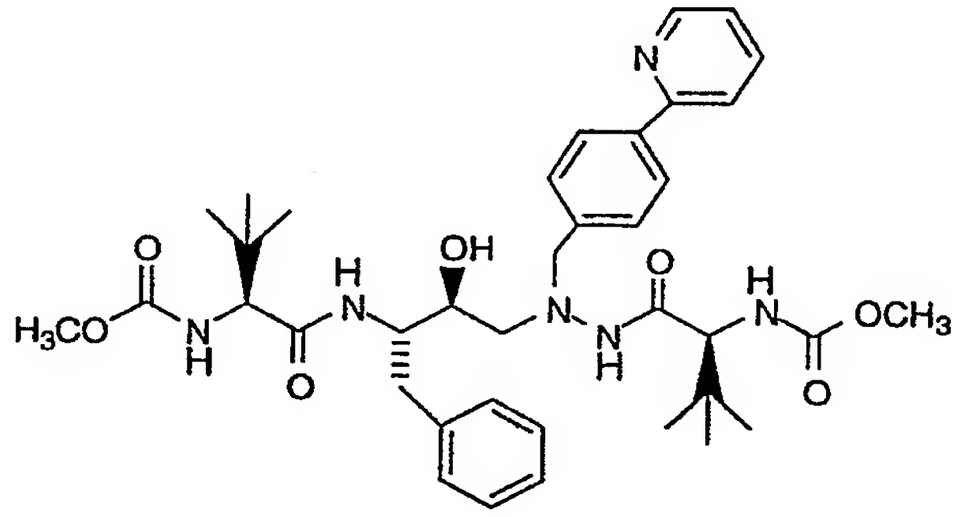
BISULFATE SALT OF HIV PROTEASE INHIBITOR

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention provides the novel crystalline bisulfate salt of the azapeptide HIV protease inhibitor of the formula



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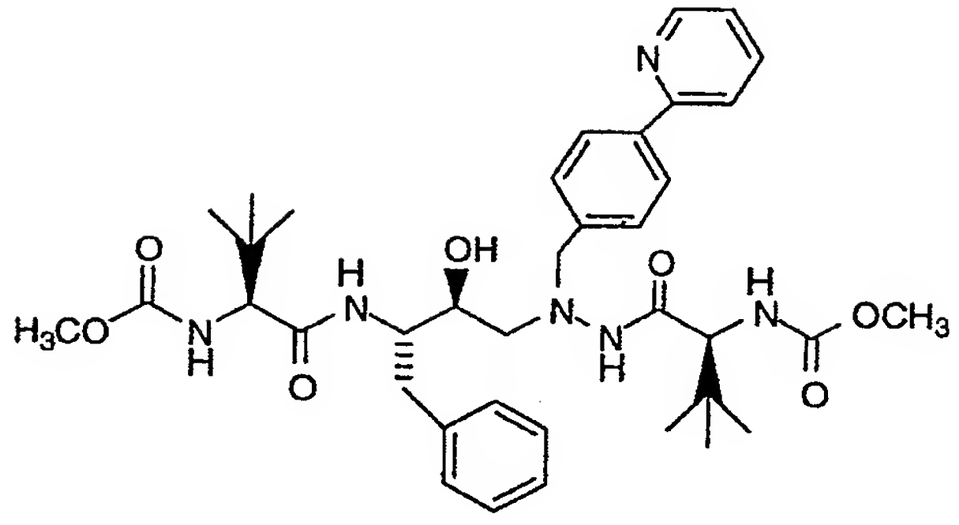
which exhibits unexpectedly superior aqueous solubility/dissolution behavior compared to other salts, and significantly improved oral bioavailability in animals compared to the free base. The bisulfate salt is thus useful for pharmaceutical dosage forms of the above-indicated protease inhibitor, particularly oral dosage forms.

2. Background Art

Published PCT patent application WO 97/40029 discloses a series of azapeptide HIV protease inhibitors reported to have a high degree of inhibitory activity against the HIV virus. One of the agents included within the scope of WO 97/40029 is the compound having the structural formula



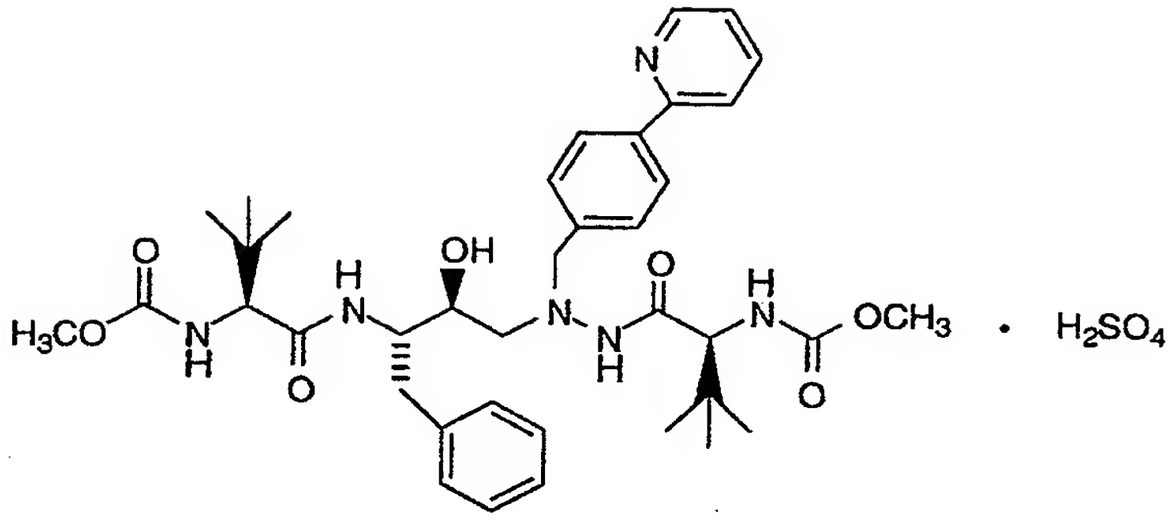
I

and the chemical name [3S-(3R*, 8'R*, 9'R*, 12R*)]-3,12-bis(1,1-dimethylethyl)- 8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)-phenylmethyl]-2,5,6,10,13-pentaazatetradecanedioic acid, dimethyl ester and is under evaluation as a possible second generation HIV protease inhibitor.

WO 97/40029 discloses the free base form of azapeptide derivatives such as compound I and also various pharmaceutically acceptable acid addition salts. While several organic and inorganic acids are mentioned as possible salt-forming agents, including sulfuric acid, there is no mention of the particular bisulfate salt which is the subject of the present application.

SUMMARY OF THE INVENTION

The present invention provides the bisulfate salt of compound I above having the structural formula



II

DETAILED DESCRIPTION OF THE INVENTION

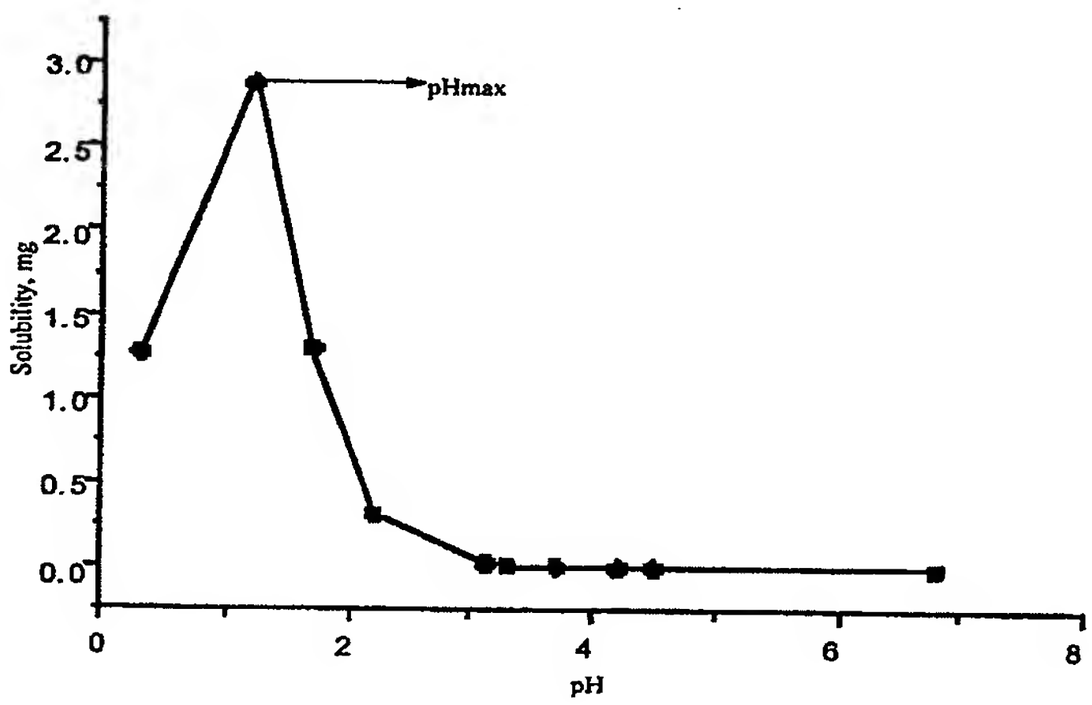
Compound I as disclosed above is a weak organic base with an aqueous solubility of less than 1 μg/mL at 24 ± 3° C. The crystalline free base form as a suspension in water or oil has poor oral bioavailability in animals, probably because of its extremely low solubility in these vehicles.

For development of pharmaceutical formulations, particularly oral dosage forms, the active ingredient must have sufficient oral bioavailability. Since the free base form of compound I did not possess such bioavailability, acid addition salts were explored by the present inventors. A number of commonly used acid addition salts such as the hydrochloride, benzenesulfonate, methanesulfonate, p-toluenesulfonate, phosphate, nitrate, 1,2-ethanedisulfonate, isethionate and sulfate were evaluated, in addition to the bisulfate salt of the present invention. All of these salts in their crystalline form exhibited lower aqueous solubility (1-3 mg/mL or less at 24 ± 3° C) than the bisulfate which had a solubility under the same conditions of approximately 4-5 mg/mL.

Solid state transformation was observed when the other acid addition salts mentioned above were suspended in water, probably due to their dissociation to form the free base. In the majority of cases, this transformation was accompanied by gel formation. Unlike the other salts mentioned above, the extra proton of the bisulfate salt prevents the conversion to the free base which, as mentioned above, is very insoluble in water and has poor oral bioavailability. The unusual solubility

behavior of the bisulfate salt in water is further elaborated in the following.

In general, conversion of salts to the unionized form or vice versa can be explained on the basis of pH-solubility theory. The solubility of the free base in water was determined as a function of pH at 24 ± 3° C and is shown below. The pH at which the compound exhibits the highest solubility is referred to as pH_{max} and was found to be approximately 1.2. It has been reported in the literature that at pH > pH_{max} of a weakly basic organic compound, the equilibrium solid phase in an aqueous suspension of the compound is the free base. At pH < pH_{max} the equilibrium solid converts to the corresponding salt form. The term "equilibrium solid phase" refers to the undissolved or excess solid in a suspension of the compound in water after sufficient equilibration time. When a salt of a weak base is equilibrated in water in an amount exceeding its solubility limit (i.e., a suspension of the salt in water), the resulting pH of the suspension may fall on either side of the pH_{max} depending on the strength of the acid among other factors. When the resulting pH is greater than the pH_{max}, the suspended solid converts to the free base.



I

Studies conducted with methane sulfonate and hydrochloride salts, in particular, of the free base confirmed the above described general findings reported in the literature. Amounts in excess of the solubility of these salts were equilibrated in water at 24 ± 3° C for at least 24 hours. The pH of the suspensions after equilibration was 2.1 ± 0.1 which is greater than the pH_{max}. The undissolved solids from these suspensions were isolated, air-dried, and characterized. By thermal and elemental analysis the undissolved solids from these suspensions were identified as the free base. This behavior was expected based on the pH-solubility profile shown in the graph above and the studies reported in the literature.

When an excess amount of the bisulfate salt was equilibrated in water a modification occurred in the solid phase in equilibrium with solution. However, the undissolved solid phase after equilibration was not the free base, although the pH (1.9 ± 0.2) of the suspension was greater than the pH_{max} and comparable to the pH of the suspensions of methane sulfonate and hydrochloride salts described above. The solid phase after at least 24 hours of equilibration was identified by elemental analysis as a hydrated form of 2:1 salt of the free base form and sulfuric acid (referred to as the sulfate salt). This behavior of the bisulfate salt is unexpected based on pH-solubility theory.

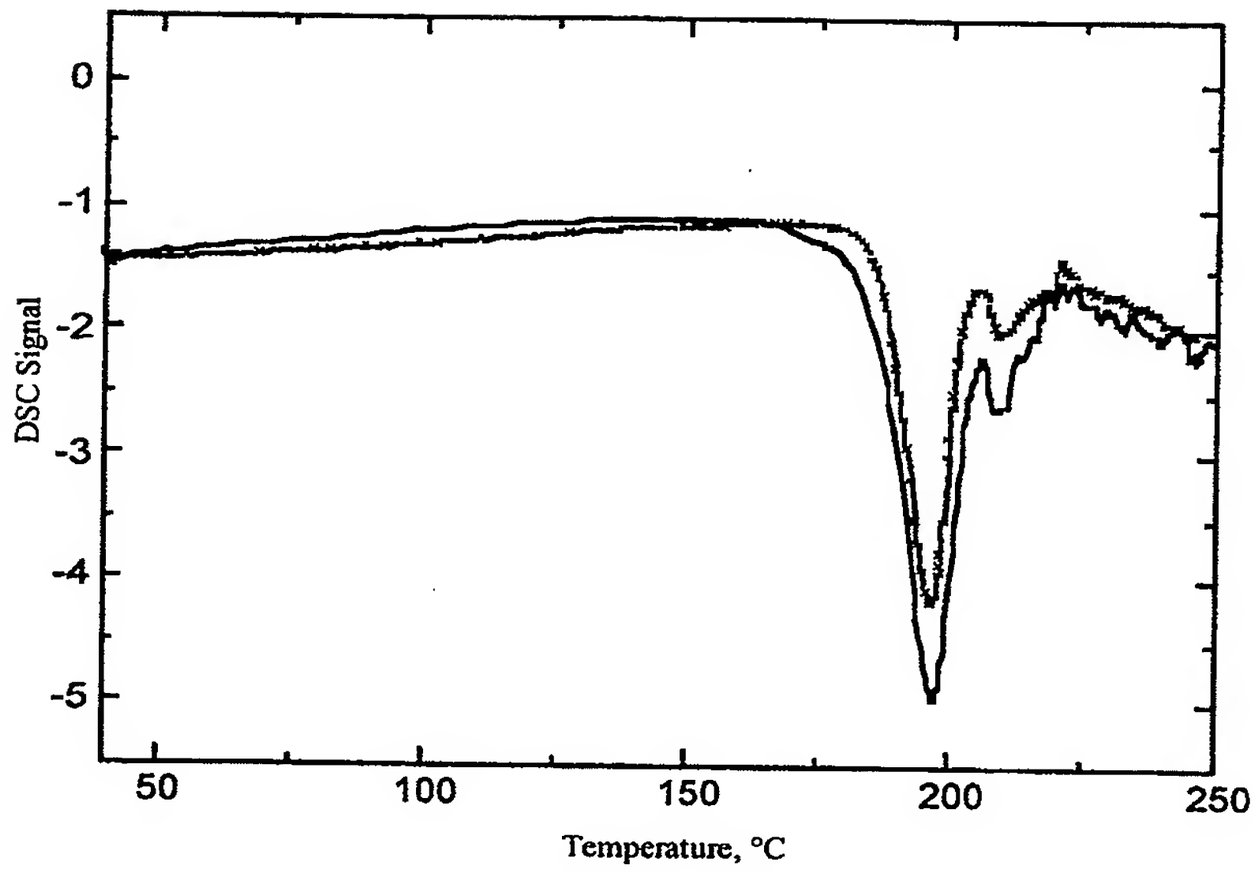
When an excess amount of the sulfate salt, in turn, was equilibrated in water a modification occured in the solid phase in equilibrium with solution. The undissolved solid from this suspension was isolated, air-dried, and characterized. Thermal and elemental analysis of this undissolved solid phase was similar to that of the free base although the conversion of the sulfate salt to the free base was not as definitive as that of the methane sulfonate and hydrochloride salts. From a pharmaceutical point of view the propensity of salts to convert to the free base in an aqueous environment is not desirable due to the low oral bioavailability of the free base. Thus, the bisulfate salt due its unique solubility behavior in water offered unexpected superiority.

The solubility behavior of the bisulfate salt in water was also unexpected considering the interaction of compound I free base and sulfuric acid in water. For example, the free base exhibited a solubility of less than 1 mg/mL in water at a pH of ~1.8 adjusted with sulfuric acid,

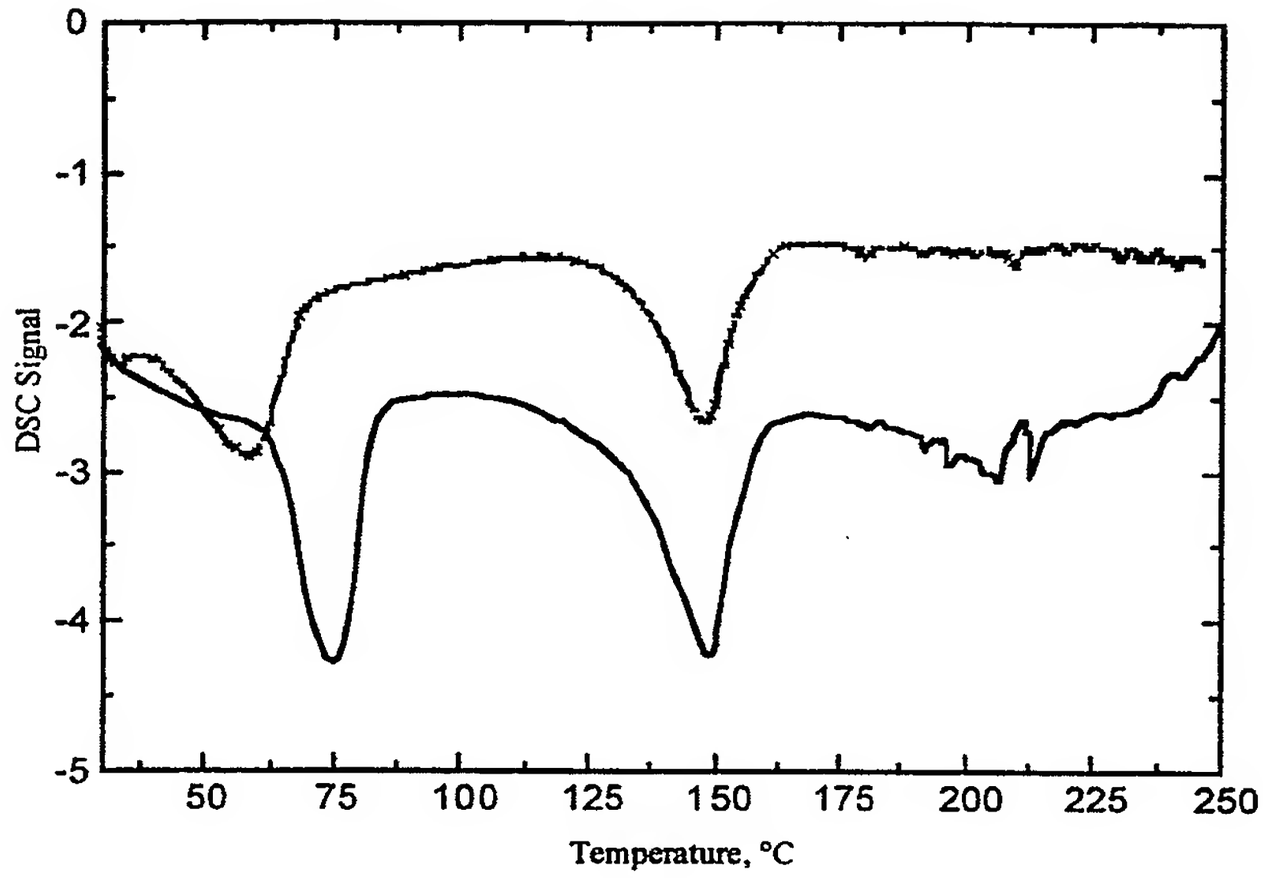
compared to 4-5 mg/mL solubility of the bisulfate salt in water at comparable pH conditions. Based on pH-solubility theory the free base and the salt are expected to exhibit similar solubility at a given pH.

The enhanced solubility/dissolution behavior of the bisulfate contributes to its improved oral bioavailability in animals relative to the free base. The absolute oral bioavailability of the bisulfate salt was found to be approximately 20% in dogs when administered in unformulated solid form placed in a gelatin capsule. In comparison, the crystalline free base had minimal oral bioavailability in dogs.

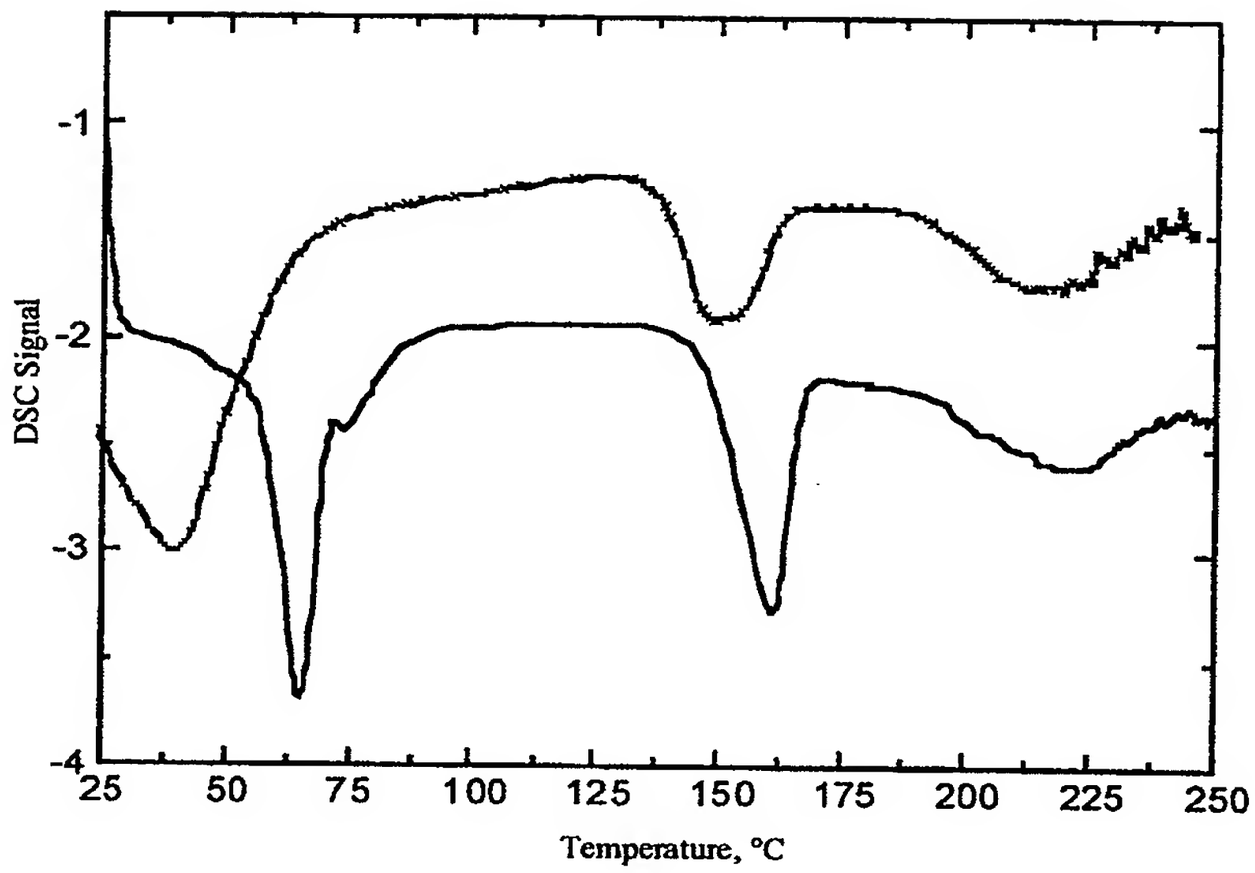
In addition to optimal solubility, satisfactory physical stability in the solid-state is another desirable property of pharmaceutical salt forms. The term physical stability indicates the ability of the salt form to retain its crystal structure (including solvents of crystallization, if any) under storage/stress conditions. Significant changes in the physical nature of the salt form as indicated by thermal methods such as differential scanning calorimetry are undesirable. The bisulfate salt exhibited excellent solid-state physical stability when stored at 40°C/75% relative humidity (RH) for as long as 9 months as shown in IIa below. Differential scanning calorimetry revealed no significant changes in the thermal behavior of the stressed sample of the bisulfate salt compared to that of the unstressed sample (stored at 2-8°C in a closed container). The methane sulfonate, hydrochloride, and the sulfate salts, on the other hand, showed significant changes in their thermal behavior when stored at 40°C/75%RH for as little as two weeks as shown in II b, c, and d. While differences in physical stability of salt forms is not unusual, the propensity of a particular salt to form solvates (or crystal modifications) and its ability to retain the solvent of crystallization (the physical stability of crystal modifications) under storage/stress conditions cannot be predicted apriori.



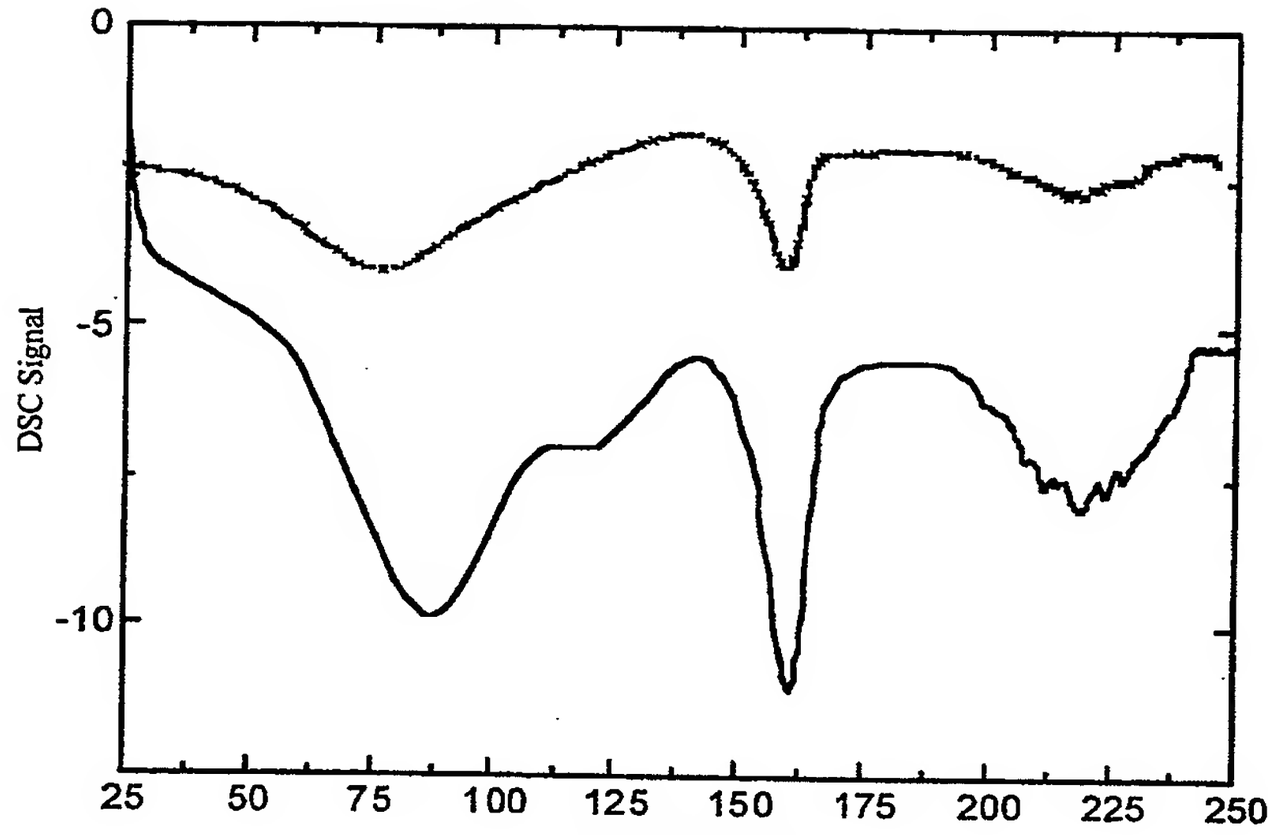
IIa. Physical stability of the bisulfate salt. The solid line represents the unstressed material. The dotted line represents the material stressed at 40°C/75% RH for 9 months.



IIb. Physical Stability of the hydrochloride salt. The solid line represents the unstressed material. The dotted line represents the material stressed at 40°C/75% RH for two weeks.



IIc. Physical stability of the methane sulfonate salt. The solid line represents the unstressed material. The dotted line represents the material stressed at 40°C/75% RH for two weeks



IId. Physical stability of the sulfate salt. The solid line represents the unstressed material. The dotted line represents the material stressed at 40°C/75% RH for two weeks.

The bisulfate salt may be prepared by forming a solution of free base of compound I with sulfuric acid in solvents such as acetonitrile, isopropanol, ethanol, or acetone and then isolating the so-produced bisulfate salt.

Because of its high bioavailability as well as its good crystallinity and stability, the bisulfate salt is very useful in preparing oral dosage forms of compound I. The examples which follow illustrate preparation of representative oral formulations.

The bisulfate salt, and formulations thereof, are used as described in WO 97/40029 for the treatment of diseases caused by viruses, especially retroviruses such as the HIV virus.

DESCRIPTION OF SPECIFIC EMBODIMENTS

Example 1

Preparation of Bisulfate Salt From Ethanol

To a 500 mL three-necked round bottomed flask equipped with an overhead stirrer and dropping funnel, 15.013 g (0.0213 mole) of free base compound I and 113 mL of 200 proof ethanol were added with stirring. To this suspension, 1.28 mL concentrated sulfuric acid was added dropwise over 90 seconds. After the addition of sulfuric acid, a clear amber-colored solution was obtained. The solution was polish filtered using #1 Whatman filter paper and washed with 5 mL of 200 proof ethanol. To this solution was added 58 mL of heptane and 37.5 mg (0.25 wt %) of seed crystals of the compound of formula II followed by 55 mL of additional heptane. The resulting mixture was stirred for 6 hours at 300 rpm. The resulting crystal slurry was filtered and washed with 50 mL ethanol/heptane (1:1) solution and dried under vacuum at 60° C overnight to afford 15.11 g of the desired crystalline bisulfate salt (88.4 mole % yield) having formula II above.

Characterizing Properties of Bisulfate Salt

Anal. Calcd. for $C_{38}H_{52}N_6O \cdot 1.0\ H_2SO_4$: C, 56.84; H, 6.78; N, 10.37; S, 3.99.
Found: C, 56.72; H, 6.65; N, 10.41; S, 3.83.
m.p. 195.0°
H_2O = 0.28% (KF)

Example 2

Preparation of Bisulfate Salt From Acetone

5M H_2SO_4 (8.52 mL, 42.6 mM) was added dropwise to a suspension of the free base compound of formula I (30.0 g., 42.6 mM) in acetone (213 mL) stirred mechanically in a 50°C oil-bath. A clear solution was obtained almost immediately. The solution was seeded with crystals of the free base compound of formula II. After two minutes, a precipitate formed which became a paste. The mixture was stirred at 50°C for one hour, at 25°C for 30 minutes and at 0°C for 2 hours. The solid was filtered and the first filtrate was used to transfer the remaining material in the flask to the filtration funnel. The product was washed with acetone, then heptane, and dried under vacuum overnight to give 31.48 g (corrected yield 92%) of the bisulfate salt of formula II, m.p. 198-199°C dec.

Anal. Calcd. $C_{38}H_{52}N_6O_7 \cdot 1.0\ H_2SO_4 \cdot 0.2\ H_2O$: C, 56.59; H, 6.80; N, 10.42; S, 3.98; H_2O, 0.45.
Found: C, 56.66; H, 6.78; N, 10.50; S, 4.20; H_2O, 0.45 (KF).

Example 3

Preparation of Bisulfate Salt From Isopropanol

Aqueous sulfuric acid (5.0 M, 0.20 mL, 1 mM) was added to a suspension of the free base compound of formula I (0.704 g, 1.00 mM) in isopropanol (4.0 mL) chilled in an ice-bath. The ice-bath was removed and the mixture stirred at room temperature. The suspension had dissolved after 15 minutes. The solution was seeded with crystals prepared as in Examples 1 or 2 above and stirred for 5 hours. The solid was filtered and the filtrate was used to transfer the solid from the flask to the funnel. The product was washed with heptane and dried under vacuum to give 0.752 g of crystalline bisulfate salt of formula II, yield 90%, m.p. 160-190°C, dec.

Anal. Calcd. for $C_{38}H_{52}N_6O_7 \cdot 1.0\ H_2SO_4 \cdot 2.0\ H_2O$; C, 54.40; H, 6.97; N, 10.02; S, 3.82; H_2O, 4.29.
Found: C, 54.25; H, 6.73; N, 10.02; S, 3.67; H_2O, 4.53 (KF).

The crystals obtained from isopropanol showed a powder x-ray diffraction pattern different from the crystals obtained from acetonitrile, ethanol-heptane or acetone. They are now referred to as Type-II crystals. The Type-I crystals appear to be an anhydrous/desolvated crystalline material while the Type-II crystals are a hydrated, hygroscopic crystalline form.

Example 4

Preparation of Capsule Formulations of Bisulfate Salt

A. Capsules (50 and 200 mg free base equivalent)

Capsules are provided for oral administration in which the capsule is a size #0, gray, opaque, hard gelatin capsule containing the bisulfate salt of formula II formulated as a wet granulation with lactose, crospovidone and magnesium stearate.

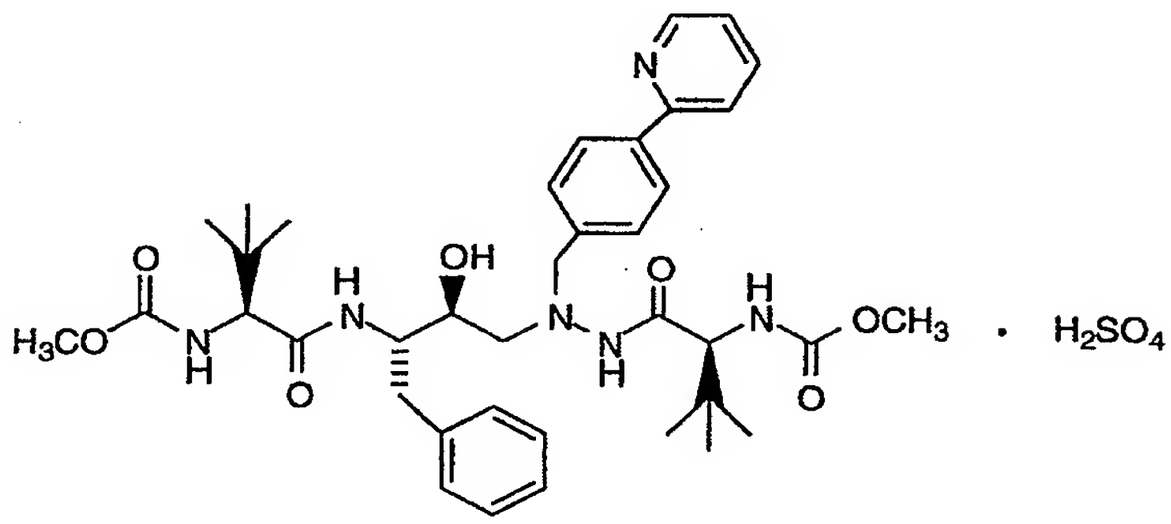
B. Capsules (100 mg free base equivalent)

Capsules are provided for oral administration in which the capsule is a size #0, gray, opaque, hard gelatin capsule containing the bisulfate salt of formula II suspended in Gelucire 44/14. Gelucire 44/14 is a saturated polyglycolized glyceride consisting of mono-, di- and triglycerides and mono- and di-fatty acid esters of polyethylene glycol. Capsules are prepared by melting Gelucire 44/14 at 45-70° C followed by addition of the bisulfate salt with stirring. The molten mixture is filled into hard gelatin capsules and allowed to cool and solidify.

CLAIMS

We claim:

1. The bisulfate salt having the formula



II

2. A pharmaceutical dosage form comprising the bisulfate salt of Claim 1 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/27382

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :C07D 213/02; A61K 31/44
US CL :514/357 ; 546/335
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/357; 546/335

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS COMPUTER SEARCH 1966-TO DATE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97/40029 A1 (NOVARTIS A.G) 30 October 1997, see entire document.	1 and 2

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
09 MARCH 1999

Date of mailing of the international search report
26 MAR 1999

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